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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Pablo Tamayo, Jill P. Mesirov, Eric S. Lander, and Todd R. Golub		
Application No.:	09/525,142	Group:	1631
Filed:	March 14, 2000	Examiner:	S. Zhou
Confirmation No.:	8330		
For:	Methods and Apparatus for Analyzing Gene Expression Data		

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on 7/10/03 Annie Demirel
Date Signature

Annie Demirel
Typed or printed name of person signing certificate

DECLARATION UNDER 37 C.F.R. §1.132 BY GABRIEL KREIMAN, M.Sc., Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Gabriel Kreiman, M.Sc., Ph.D. of Cambridge, Massachusetts declare and state that:

1. I am currently a Whiteman Fellow at the Center of Biological and Computation Learning at the Massachusetts Institute of Technology. I obtained a Ph.D. in Biology and a M.Sc. in Computation and Neural Systems from Californian Institute of

Technology under Professor Christof Koch, and a B.Sc. in Physical Chemistry with Honors from the University of Buenos Aires. I have published a number of journal articles on the subject of bioinformatics. I have also received a number of awards for scientific achievement. My *Curriculum Vitae* is attached as Exhibit A.

2. I have no ownership interest in the above-referenced application. I am not being compensated for providing this Declaration.

3. Prior to making this Declaration, I have reviewed the specification, office action dated February 11, 2003, and references cited in this office action for the above-referenced application. The references that I have reviewed include, but are not limited to, U.S. Patent No.: 6, 303, 301 (Reference A of PTO-Form 892 dated 5/22/02, hereinafter "Mack"); Mangiameli *et al., European J. Operational Res.* (93): 402-417 (1996) (Reference U of PTO-Form 892 dated 05/07/01, hereinafter "Mangiameli"); and Kohonen, T., *Self-Organizing Maps*, 2nd Edition, T.S. Huang et al., eds. (NY: Springer-Verlag, 1997) (Reference AR of IDS filed 7/24/00 hereinafter "Kohonen").

4. On page 4 of the February 11, 2003 office action, the Examiner states:

> As set forth in the previous Office action, while Mack reference does not explicitly teach or suggest use of SOM for the data analysis, it does motivate/suggest using alternative statistical methods (see columns 27-28). More importantly, the motivation to modify Mack comes from Mangiameli, who, after comparing SOM and seven clustering methods, concludes that SOM is superior to all others in determination of natural subgroups in a data set. Given the large number of genes used in Mack (65,000 for potential genes regulated by p53), one of ordinary skill in the art would have been motivated by Mangiameli to modify Mack by using SOM instead of cluster analysis.

5. I respectfully disagree with the Examiner's conclusion for the reasons presented below.

6. While the self organizing maps (SOMs), described by Kohonen and Mangiameli, have been used for quite some time now, the application of this tool to the study of gene expression data is novel and has unexpected, surprising results. The application of SOMs to gene expression data is the subject of the claimed invention, and is attributed to the inventors, Tamayo *et al.* The inventors have successfully used this tool in the study and classification of gene expression among different types of cancer cell types.

7. Mack has provided computational tools for the analysis of microarray data. Mack only generally refers to clustering methods, and does not suggest using an unsupervised clustering method. For example, in Column 27, Mack only quotes some very general cluster books:

> "Methods for cluster analysis are described in detail in Harfigan (1975) *Clustering Algorithms*, NY, John Wile and Sons, Inc, and Everritt, (1980) *Cluster Analysis 2nd. Ed.* London Heineman Educational books, Ltd., incorporated herein for all purposed by reference. The causal relationships in a genetic network can also be modeled by stochastic procedures. Such models allow the examination of the dynamical aspects of the genetic network in terms of change over time or across conditions. Maybeck, *Stochastic Models, estimation and control, vol.* 1, (1979) NY, Academic Press.

Thus, Mack only generally refers to the use of clustering methods and does not disclose how they specifically accomplished the clustering of the data. Numerous papers have been published proposing different algorithms, and different algorithms and computational tools may serve different purposes. I would not read the generalizations in Mack, in combination with the other cited references, and come to realize the specific direction of the claimed invention, namely to use an unsupervised clustering algorithm of SOM to analyze gene expression data.

8. Mack provides methods for mapping regulatory relationship among genes by using supervised clustering where the number of clusters as well as their composition are determined by the scientist beforehand. The supervised clustering, as generally described in Mack, refers to the need for the user to input information into a computer before the algorithm can be used to determine the results. Supervised clustering, like that described in Mack, is one that involves the predetermination of the number of clusters as well as their composition. In contrast, the claimed invention of Tamayo *et al.* uses unsupervised clustering, which generally does not require user input, and the algorithm can analyze the data independently. An important distinction between Mack and the claimed invention is that the claimed invention does not require prior knowledge of the data, whereas Mack does. Additionally, For example, Mack states "in some embodiments, models are built by incorporating expression data and current knowledge about the regulation of specific genes." Column 27. As stated above, I did not find an example in Mack in which unsupervised learning was used. As such, I would not have combined Mack which describes supervised clustering with Mangiameli and Kohonen which describe the use of SOM, an algorithm utilized in unsupervised learning, to analyze gene expression data.

9. Additionally, on page 4 of the subject office action, the Examiner states:

> Indeed, one embodiment of Mack's invention is a method to determine what genes are regulated by a gene, say, p53. See column 29. The method comprises taking samples from such cells containing p53 mutation and normal cells in parallel, analyzing the expression level of plurality of genes, 65,000 in the case of p53, clustering and categorizing genes based on their expression level, and building causal model.

The Examiner further states:

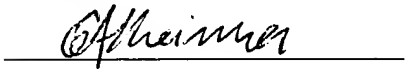
> Only after cluster analysis is done, by comparing the clusters of p53 mutation and wild type, a model is obtained for genes regulated by p53. Thus, for the clustering analysis step, Mack does not require prior knowledge of any relationship of the genes tested from p53. On

the contrary, one of the purposes for Mack is to determine the relationship of genes of 65,000 with p53.

10. As described above in Paragraph 8, Mack involves supervised clustering. As such, I interpret the experimental section represented in paragraph 9 to mean that at some point the user will select a predetermined number of clusters and assume some knowledge about the methodology. Although Mack does set out to determine the relationship of genes, certain knowledge is assumed and used to determine this relationship.

11. Mack, when combined with Mangiameli and Kohonen, does not amount to the claimed invention. The combined references in fact, leave the following long-felt needs: (i) the need for more sophisticated tools (e.g., accurate assessment of statistical significance of results, different types of boundaries for clusters, etc.), (ii) the need to analyze different aspects of the data (e.g., time series data sets, comparison of different conditions, etc.), and (iii) the need for unsupervised clustering tools. To this end, the claimed invention has fulfilled these long-felt needs and has provided the Bioinformatics and Genetics communities with a very valuable and novel tool to analyze gene expression data, a tool not described by the cited references.

12. I further declare that all statements made herein of my knowledge are true and that all statements made on other information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Gabriel Kreiman, M.Sc., Ph.D.

July 3, 2003

Date

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kreiman@mit.edu

Education

1996-2001	Ph.D. California Institute of Technology. *Biology Division.* Advisor: Professor Christof Koch
1998-2001	M.Sc. California Institute of Technology. *Computation and Neural Systems*. Advisor: Professor Christof Koch
1991-1996	B.Sc. With Honors. University of Buenos Aires. *Physical Chemistry*

Work experience (brief)

2002-present	Whiteman Research Fellow. Massachusetts Institute of Technology.
2001-2002	Staff Scientist, Genomics Institute of the Novartis Research Foundation
1996-2001	M.Sc. and Ph.D., California Institute of Technology

Journal publications

1. **Kreiman G**, Fried I, Koch C. (2002) Single neuron responses in the human brain during flash suppression *Proceedings of the National Academy of Science USA,* **99**:8378-8383
2. Krahe R., **Kreiman G.**, Gabbiani F., Koch C. and Metzner W. (2002) Stimulus encoding and feature extraction by multiple pyramidal cells in the hindbrain of weakly electric fish. *Journal of Neuroscience*, **22**:2374-2382.
3. Rees G., **Kreiman G.** and Koch C. (2002) Neural correlates of consciousness in humans. *Nature Reviews Neuroscience*, **3**:261-270.
4. Zirlinger M., **Kreiman G.** and Anderson D. (2001). Amygdala-enriched genes identified by microarray technology are restricted to specific amygdaloid sub-nuclei. *Proc. Nat. Acad. Sci.,* **98**:5270-5275.
5. **Kreiman G.**, Koch C. and Fried I. (2000). Imagery neurons in the human brain. *Nature,* **408**:357-361. {see also *Highlight*:: Collins P. (2001). *Nature Reviews Neuroscience,* **2**, 9-9}
6. **Kreiman G.**, Krahe R., Metzner W., Koch C. and Gabbiani F. (2000). Robustness and variability of neuronal coding by amplitude sensitive afferents in the weakly electric fish *Eigenmannia*. *Journal of Neurophysiology,* **84**:189-204.
7. **Kreiman G.**, Koch C. and Fried I. (2000). Category-specific visual responses of single neurons in the human medial temporal lobe. *Nature Neuroscience,* **3**:946-953. {see also News and Views: Gross, C. (2000). *Nature Neuroscience,* **3**, 855-856}
8. Ouyang Y., Rosenstein A., **Kreiman G.**, Schuman E. M. and Kennedy M. B. (1999). Tetanic stimulation leads to increased accumulation of CaMKII via dendritic protein synthesis in hippocampal neurons. *Journal of Neuroscience,* **19**:7823-7833.
9. Inon de Iannino N., Briones G., **Kreiman G.** and Ugalde R. (1996). Characterization of the biosynthesis of β(1-2) cyclic glucan in *R. Freddii. Cell. and Mol.. Biol.,* **42**:617-629.

Selected abstracts and other publications

1. Kreiman G., Koch C., Fried I. (2002). Sparse representation of visual information by single neurons in the human medial temporal lobe. *Annual Meeting of the Cognitive Neuroscience Society, San Francisco.*
2. Krahe R., Kreiman G., Gabbiani F., Koch C., Metzner W. (2002) Feature extraction by multiple neurons in a topographical sensory map. *Computational Neuroscience.*
3. Kreiman, G. (2001). On the neuronal activity in the human brain during visual recognition, imagery and binocular rivalry. Ph.D. Thesis. Department of Biology, California Institute of Technology, Pasadena.

EXHIBIT

A

4. Kreiman, G. (2001). Neural coding and feature extraction of time-varying signals. M.Sc. Thesis. Computation and Neural Systems, California Institute of Technology, Pasadena.
5. Kreiman, G. (2001) Moveo ergo sum. *BioEssays* **23**:662 (Book Review).
6. Kreiman, G., Fried, I., Koch, C. (2001) In *Annual Meeting Visual Sciences Society,* Sarasota. Single neuron responses in humans during binocular rivalry and flash suppression.
7. Krahe R., Kreiman G., Gabbiani, F., Koch, C. and Metzner, W. (2001). Information transmission by multiple pyramidal cells in the electrosensory lateral line lobe (ELL) of the weakly electric fish, *Eigenmannia*. In *International Society of Neuroethology*. Bonn. *Journal of Physiology, In Press*.
8. Kreiman, G., Staba, R., Wilson, C. and Fried, I. (2001). Synchrony between single neurons in the human brain during sleep. In *Annual Meeting of the Society for Neuroscience*, San Diego, Vol. 27
9. Kreiman, G., Fried, I. and Koch, C. (2000). Category-specific visual responses of single neurons in the human medial temporal lobe. In *Annual Meeting of the Society for Neuroscience*, New Orleans, Vol. 26.
10. Kreiman, G., Fried, I. and Koch, C. (2000). Imagery neurons in the human brain: A proposed substrate for visual experiential phenomena in epilepsy. In *American Epilepsy Society,* Los Angeles. *Epilepsia* **41S**:32-32.
11. Krahe, R., Kreiman, G., Gabbiani, F., Koch, C. and Metzner, W. (2000). Feature extraction by multiple pyramidal cells in the hindbrain of weakly electric fish. In *European Neuroscience Societies Annual Meeting*, Brighton, UK. *European Journal of Neuroscience*, **12S**:90-90.
12. Kreiman, G., Koch, C. and Fried, I. (2000). Responses of single neurons in the human brain during visual presentation and imagery. In *Cognitive Neuroscience Society*, San Francisco. *J. Cogn. Neurosci.* **S**:70-70.
13. Kreiman, G. and Koch, C. (1999). Flash Suppression: Competition Between Eyes or Patterns? In Research in Vision and Opthalmology, Fort Lauderdale, *Investigative Opthalmology and Visual Science* **40S**:421-421.
14. Kreiman, G., Gabbiani, F., Metzner, W. and Koch, C. (1999). Robustness, variability and modeling of amplitude modulation encoding by P-receptor afferent spike trains of weakly electric fish. In *Neural Information and Coding Workshop.* Big Sky, Montana.
15. Kreiman, G., Gabbiani, F., Metzner, W. and Koch, C. (1999). Robustness and Variability of the neural code in P-receptor afferents of *Eigenmannia* electric fish. In *Frontiers in Computational Neuroscience,* Eilat, Israel.
16. Kreiman, G., Gabbiani, F., Metzner, W. and Koch, C. (1998). Noise in *Eigenmannia* P-receptors. In *Dynamical Neuroscience Satellite Symposium*, Los Angeles.

Selected awards and honors

2002	Milton and Francis Clauser Doctoral Prize, Caltech. Best Ph.D. Thesis.
2002	Lawrence L. and Audrey W. Ferguzon Prize, Caltech. Best Biology Ph.D. Thesis.
2000	Everhart Distinguished Graduate Student Lecture Award. Caltech.
1997	Argentine Chemistry Association Honor Award
1995	A. Luna Honor Award. Dow Chemical Company.
1994	Outstanding Youth Award. Buenos Aires Stock Exchange Foundation.
1990	Sub-champion. National Math Olympiads. Argentina.
1984	Metropolitan Chess Champion. Buenos Aires. Argentina.

Teaching experience

Instructor

1999-2000 CNS/Bi 163, Created and taught Caltech course (undergrad/grad. level).

Teaching assistant

1997-1998 Bi 8, CNS/Bi162. Caltech.
1993-1996 Physical Chemistry. UBA.

Additional information

Professional societies

Soc. for Neurosci., Cogn. Neurosci. Soc., American Assoc. for the Advanc. of Science, Vision Sciences Soc.

Computing experience (brief)

- MATLAB, C/C++, Java, HTML, Perl, Windows, Linux, Unix
- *Designed Spiker*: clustering software
- *Designed Gene_screen*: software for analysis of DNA microarray data

Extra-curricular activities

- Volunteer Scientist. Science-By-Mail Program. 1998-2000.
- Graduate Student Council. Biology Representative. Caltech. *1997-1998*
- Leloir Institute Research Board. Chemistry Undergrad. Representative. *1995-1996*